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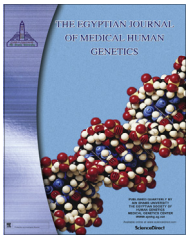

ORIGINAL ARTICLE

Challenges identified in the management of patients with inherited metabolic disorders – A five year experience from Pakistan

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KEYWORDS

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Abstract *Background:* Pakistan is the sixth most populous country in the World. High rates of consanguinity and inter caste marriages have resulted in a substantial burden of inherited metabolic disorders (IMDs). Despite this load, there is a dearth of both medical genetic and clinical metabolic services in Pakistan. There are inadequate numbers of appropriately trained clinicians, ill-equipped laboratories, lack of scientists and technologists equipped with skills to deal with the challenging laboratory investigations involved in IMD and a health care infra-structure unable to support a service.

Aim: We present the first five year experience of the first established metabolic unit at a tertiary care hospital in Pakistan and present the case for screening of parents, parents' siblings and antenatal diagnostic testing in subsequent pregnancies in order that families can make informed choices in preventing recurrence.

Subjects and methods: This retrospective observational study comprising of patients' chart review was conducted in the Department of Paediatrics, AKUH Karachi in Pakistan for patients who presented to the Clinical Genetics unit from January 2008 to December 2012 seeking diagnosis and treatment for the underlying IMD.

Results: We evaluated 426 children, of which, 333 (78%) had consanguineous parents. Most patients, 151 (35%). evaluated for IMD were between 1 year and 5 years of age. Developmental delay, seizures, hypotonia, microcephaly, neuroregression, dystonia, ataxia and encephalopathy

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were the most common reasons for referrals. Only 155 (36%) patients underwent metabolic biochemical testing. Among the investigated group of patients, diagnoses were established for 85 (55%) patients equivalent to only 19.8% of the total.

Conclusion: Neonatal screening for IMDs and their treatment in the current situation is an unaffordable practical option in Pakistan. Screening parents, siblings and subsequent pregnancies, however, is likely to provide a cost effective and acceptable alternative in reducing the burden and enabling early, effective detection of affected progeny before the stage when neurometabolic changes become irreversible in developing countries like Pakistan with very limited resources.

1. Introduction

Inherited metabolic disorders (IMDs) encompass a group of disorders due to defective metabolic processes. The Cumulative incidence of IEMs varies between 1 in 1400 in British Columbia [1] and 1 in 3000 in Germany [2]. The measured prevalence in a particular country depends on the population selected for screening and the method employed for screening for IMDs. With the drop in communicable diseases in developed countries, a demographic switch from communicable diseases to genetic disorders is being observed in many developed countries. However, establishment of programs for the systematic detection of IMDs in developing countries has been a challenging process [3]. Pakistan faces major health challenges with high population growth, fertility, and high infant and under-five mortality. There is uncontrolled burden of communicable diseases with an increasing problem of non-communicable diseases, which comprised 44% of top 10 causes of mortality/-morbidity in 2010 [4]. This has resulted in not only lack of government commitment to invest in this orphan group of diseases but also instilled a belief among physicians in Pakistan that IMDs are rare diseases, which are untreatable and the feeling that creating a service does not represent a good use of already overstretched resources.

The objective of this descriptive study is to report the five year experience of the first established metabolic unit at a tertiary care hospital in Pakistan. We describe the spectrum of IMDs seen, challenges faced in reaching a diagnosis, and difficulties encountered in treatment and follow-up. We also propose some tangible solutions to the unique challenges faced in establishing genetic and metabolic services in Pakistan.

2. Pakistan and its health care structure

Pakistan is a South Asian country and the sixth most populous nation in the World, having a population of over 184 million [5]. The country has four provinces; Punjab, Sindh, Khyber Pakhtunkhwa and Balochistan. The population comprises of six major ethnic subsets including Punjabis 44.68%, Pathans 15.42%, Sindhis 14.1%, Sariakis 8.38%, Muhajirs 7.57%, Balochis 3.57% and others 6.28%. Punjabis and Sariakis are mostly residing in Punjab province, Sindhis and Muhajirs in Sindh province, Pathans in Kyber Pakhtunkhwa and Balochis in Balochistan province [6]. Consanguineous marriages and endogamy are prevalent in Pakistan irrespective of socio-economic and educational background of different ethnicities. Consanguinity is present in 65% of all marriages [7] and is a major contributor to both early and late morbidity and mortality [8].

The WHO has identified Pakistan as one of 57 countries with critical shortages of health care providers across the globe [3]. The physician to 1000 person ratio in Pakistan is 0.8 as compared to 2.4 in USA [9] and the total per capita health expenditure for Pakistan is USD 39 as compared to USD 8895 in USA [10]. Health care management in Pakistan is primarily the responsibility of the provincial government. However, planning and formulation of national health policies are under the federal government's control. The health care system is dichotomized into a small under-utilized public sector financed by the state and a large independent for profit private sector that accounts for 80% of all outpatient health care [11], for which patients have to pay out of pocket. Thirty-four percent of the population is urban having some access to effective health care services [12].

3. Current status of inherited metabolic disorders in Pakistan

Infant and under five mortality rates of Pakistan are 74 per 1000 and 89 per 1000 live births [7]. Birth asphyxia, still birth, pneumonia, diarrhea, sepsis, neonatal tetanus and congenital birth defects are attributed major causes of neonatal and infant mortality in developing countries [13]. Partly as a result of the attention afforded to these problems, IMDs have been relatively ignored by both the government as well as the private sector. There is no national birth defect or metabolic diseases registry established in Pakistan nor is there a newborn screening program for any IMD in any of the four provinces. Before 2013, only rudimentary metabolic testing was available and though this has recently marginally expanded, there is little clinical expertise available for diagnosing and treating patients with IMDs. Treatment options in the form of food for special medical purpose (FSMP) and the availability of orphan drugs is a constant challenge. These factors have resulted in a difficult situation for physicians, parents and families many of whom are faced with a gloomy prognosis when given a diagnosis of a 'non-specific IMD' with little or no counseling about the prognosis or inheritance of the disease. Consequently, most cases are undiagnosed and result in either death or irreversible psychomotor retardation.

In this backdrop, the Clinical Genetics Unit was established by the Department of Paediatrics and Child Health, Aga Khan University in October 2007. Housed with a trained staff geneticist, it is the only nationwide institute providing comprehensive and evidence based medical care to patients with IEMs. The Aga Khan University Hospital (AKUH) is a

philanthropic non-profit hospital in the metropolitan city of Karachi, the hub of industry and business and thus populated by diverse ethnicities from all over the country. Being the largest medical facility of Pakistan with many well-developed sub-specialties it provides diagnostic and treatment facilities to not only the population of Karachi but to referral cases from across the country as well as from neighboring countries. Thus the patient population coming to AKUH represents the diversity of ethnicities in the country.

4. Subjects and methods

4.1. Study design

Retrospective notes review.

4.2. Study setting

The study was set in Department of Paediatrics, AKUH Karachi in Pakistan. Pakistan is classified as a low-middle income country in the World Bank List of economies (April 2012). During the 5 year period from January 2008 to December 2012, no diagnostic tests for IMDs were undertaken in Pakistan. All laboratory tests were sent to Malaysia and analyzed at the Institute of Medical Research, Kuala Lumpur.

4.3. Study methods

This study is a chart review of patients who presented to the Clinical Genetics Unit from January 2008 to December 2012 seeking diagnosis and treatment for their underlying IMD. Information for the patients including age of presentation, gender, consanguinity of parents, referring discipline, whether patients were referred with a definite diagnosis or not and reasons for referral was extracted from the charts and entered into a structured questionnaire after approval from Institutional Ethics Review Committee (Number 3177-PED-ERC-14). As this is an exploratory study, only percentages and proportions are reported.

5. Results

During the five year period, a total 1019 patients were seen in the Clinical Genetics Unit of Department of Paediatrics, Aga Khan University Hospital. This included 329 patients with genetic disorders, 264 couples seeking antenatal or pre-marital genetic counseling and 426 patients with IEMs. This paper is focused on the cohort of IMD patients. The majority of patients seen were born to consanguineous parents, 333 (78%) with a male predominance of 255 (60%). Age was stratified into five groups including neonates (< 1 month), infants (1 month to less than 12 months), 1 year to less than 5 years, 5 years to less than 10 years and children greater than 10 years of age. The majority of patients evaluated for IMDs were in the 1–5 years age group, which was 151 (35%). The distribution of patients according to age is shown in Fig. 1. The neurological symptoms including developmental delay/psychomotor retardation, seizures, hypotonia, microcephaly, neuroregression, dystonia, ataxia and encephalopathy were the most frequent reasons for referral to the Clinical Genetics Unit. The ten most frequent reasons for referral observed in patients are listed in Table 1. Combination of these symptoms and signs were seen in most patients. More than one symptom and sign was often observed in most patients. A positive family history of a sib with psychomotor retardation or death was the third most common reason to seek medical help, which was observed in 95 (22%) of patients. The main sources of referral were general pediatricians (33%); and neurologists (23.5%). Other referring disciplines were cardiology, infectious diseases, dermatology and hematology departments. Only 42 (10%) patients were referred with a pre-existing diagnosis. Of the 426 IMD patients seen during the study period, parents of only 155 (36%) agreed for limited metabolic testing while the majority 271 (64%) parents declined any testing. Among the investigated group of patients, diagnoses were established for 85 (55%) patients equivalent to only 19.8% of the total. In 95% of these 85 patients, a treatable disorder was identified with only 5% being found to be non-treatable. The non-treatable diseases included lysosomal storage disorders (LSDs) with 2 patients each with GM1 gangliosidosis and Farber disease. Other than these 4 non-treatable LSD patients, 17 treatable LSD were diagnosed. However, due to the high cost of enzyme replacement therapy for these treatable LSDs, these patients could not afford treatment. Thus for practical reasons, in this paper, the word "treatable" is limited to diseases like glycogen storage disorders (GSDs), organic academia, urea cycle defects, vitamin responsive disorders and fatty acid oxidation defects. In the "treatable group" 60 patients were included. The spectrum of diseases, with the number of patients with each disease is summarized in Table 2. The diagnoses were made on the basis of biochemical

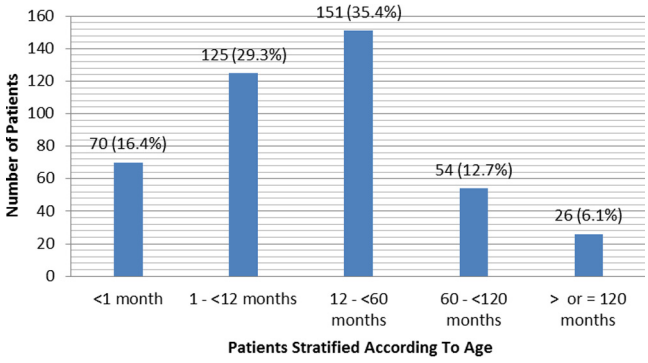

Figure 1 Patient distribution according to age.

Table 1 Top ten reasons of referral to metabolic unit.

Clinical criteria	Percentage of 426 patients referred
Psychomotor retardation	155 (36.4%)
Seizures	101 (23.7%)
Family history of sibling with psychomotor retardation or death	95 (22.3%)
Coarse facies	61 (14.3%)
Hypotonia	57 (13.4%)
Failure to thrive	39 (9.2%)
Vomiting	31 (7.3%)
Microcephaly	26 (6.1%)
Neuroregression	26 (6.1%)
Dystonia	22 (5.2%)

Table 2 Spectrum of IMD in 85 diagnosed patients out of 426 patients who completed investigation.

Group	IMD	Number of patients
Carbohydrate metabolism	Glycogen storage disorders	
	Type I (a)	2
	Type III	2
	Unspecified type	4
	Fructose 1,6 bisphosphatase deficiency	4
	Fanconi–Bickel syndrome	2
Lysosomal disorder	Mucopolysaccharidosis	
	Type I	2
	Type II	2
	Type III	3
	Unspecified type	6
	Gauchers disease	4
	Farber disease	2
	GM1 gangliosidosis	2
Organic acidemia	Methylmalonic acidemia	8
	Propionic academia	4
	Glutaric aciduria type I	3
	Isovaleric acidemia	2
	3-Hydroxy-isobutyric aciduria	1
Vitamin responsive disorder	Intracellular Cb1C defect	4
	Biotinidase deficiency	4
	Holocarboxylase synthetase deficiency	1
Fatty acid oxidation and carnitine shuttle defects	Medium chain acyl CoA dehydrogenase deficiency	3
	Carnitine palmitoyl-transferase type 2 deficiency	2
	Long chain acyl CoA dehydrogenase deficiency	1
	Carnitine transporter defect	1
Aminoacidopathies and urea cycle defect	Cystathionine beta synthetase deficiency	4
	Urea cycle defects	3
	Tyrosinemia-type I	2
	Alkaptonuria	2
Ketogenesis and ketolytic defects	Betaketothiolyase deficiency	3
	3-Hydroxy-3-methylglutaryl CoA lyase deficiency	2
Total		85

test and enzyme assays, but due to the limited availability and cost of specialized laboratory tests, the specific type of GSDs or mucopolysaccharidosis (MPS) was only discernable in about half of these patients. Out of these 60 patients, 6 (10%) died during the five year period. More than half; 34 (57%) did not continue treatment and were lost to follow-up, whereas only 20 (33%) were treated and are under regular follow-up for five years representing only 4.7% of the original total (Fig. 2).

6. Discussion

This is the first study reporting systematic and organized data of patients with IMDs over five years from the only Clinical Genetics Unit in Pakistan. This study was conducted in the period when there was no infrastructure available for diagnostic tests locally and all tests were sent to overseas laboratories. About two-thirds of the patients declined any kind of investigations due to the high cost involved in testing and transportation of samples to overseas labs.

Of those with treatable IMDs, 57% were unable to continue treatment due to multiple reasons including local non-availability of FSMP and medicines; parents inability to import FSMP and medicines on a regular basis; expense of both, high customs duty imposed by government on the import of the FSMP and medicines, which they were supposed to pay out-of-pocket till their children were able to support their own treatment. Patients with IMDs often require frequent hospitalizations, adding an extra financial challenge to families in the current health care system in Pakistan. IMD requiring FSMP is a life-long necessity for a patient, which becomes enormous. This coerces parents to not only withdraw treatment but also demand antenatal testing for genetic disorders including IMD.

It is a general perception that antenatal testing followed by selective termination of pregnancy (TOP) will be unacceptable in a Muslim country like Pakistan. According to Islamic teachings, human life begins with the inspiration of the soul, which according to the Holy Qur'an and Prophet Mohammad teaching is stated to be at the 120th day from the moment of conception. Prenatal diagnosis and TOP is allowed before 120 days of gestation if the fetus has a fatal condition such that its life would be a calamity for both the family and itself [14]. The colonial-era Penal Code of 1860 with respect to abortion was

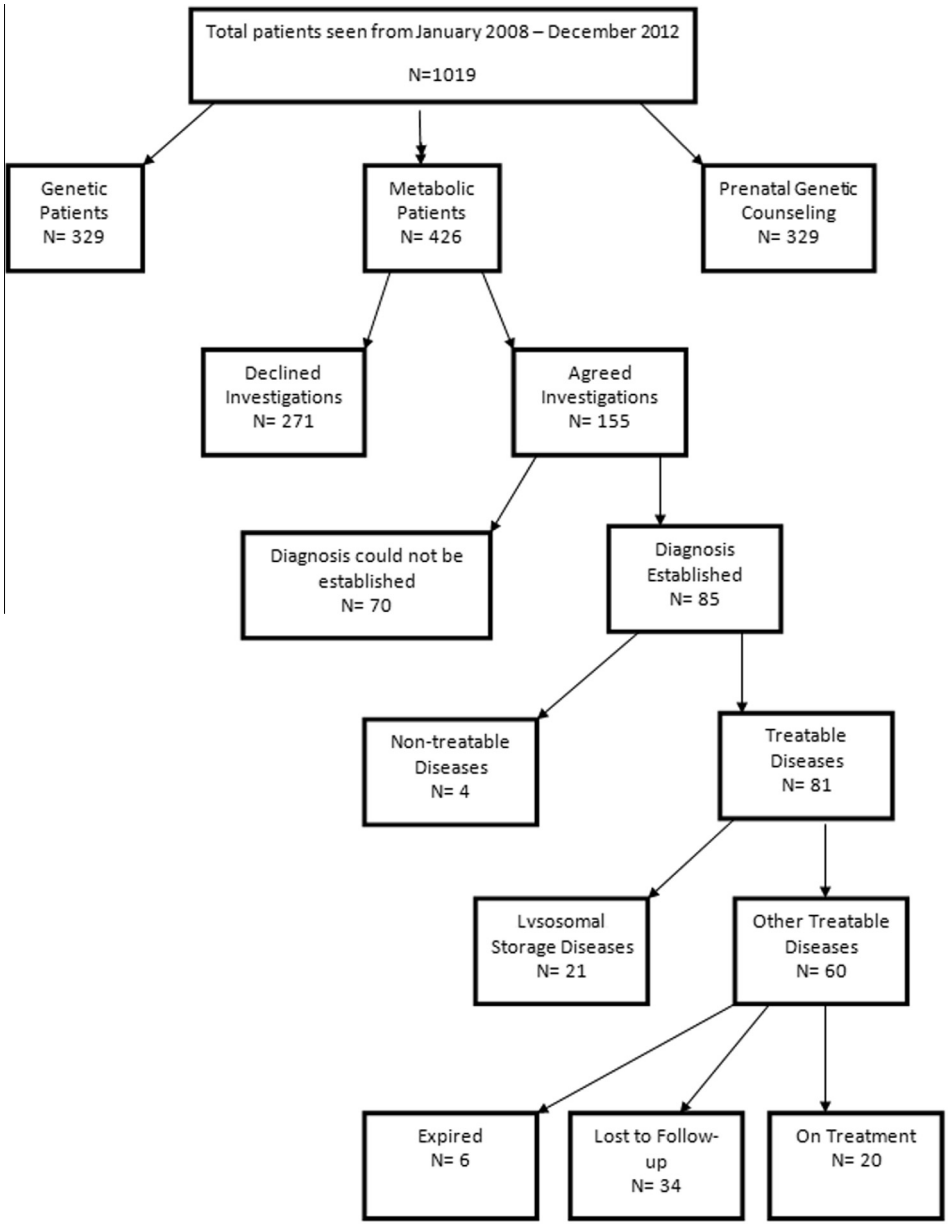

Figure 2 Flow chart showing patients seen, diagnosed and followed in five year period at the Clinical Genetics Unit, Aga Khan University Hospital.

revised by the government of Pakistan in 1990. Under, which in section 338 of the Pakistan Penal code, the conditions for legal abortion depend on the developmental stage of the fetus; whether the fetus's organs are formed or not. Islamic scholars have usually considered the fetus's organs to be formed by 120 days of gestation. Before 120 days of gestation, abortions are permitted to save the woman's life or in order to provide "necessary treatment." However, the term "necessary treatment" is not clearly defined in law and is open for interpretation [15]. In our setting, parent's complex attitude and practices are observed with reference to TOP. The corresponding author has reported 22% voluntary TOP without antenatal testing for a possible underlying genetic disorder [16]. These TOPs were opted by parents because of their anxiety and fear of having another child with a genetic disorder. They had experienced the misery of their previous child, financial challenges to coupe the needs of a special child and poor availability of multi-disciplinary support system needed for such disorders. This experience exhibits 7.5 times higher TOP rates secondary to possible genetic disorders than the overall TOP rates reported in Pakistan, which is 29 per 1000 women of reproductive age [17].

The tradition of consanguineous marriages in Pakistan is unlikely to change, thus requiring management of these disorders at considerable financial cost. At present a heavy tax is imposed on the FSMP purposed by the government, thus the current estimated annual treatment cost is about USD 15,000 for most organic acidemias and amino acidopathies. This huge cost in comparison to the estimated cost of antenatal genetic testing (about USD 2500–3000) is more non-affordable, making antenatal genetic testing as a much acceptable option to parents. Cost effective preventive programs;

including antenatal genetic testing and "cascade screening"; premarital carrier testing for the siblings of the progeny and parent's siblings for IMDs is the need in Pakistan. In communities with high consanguinity and large family size, cascade screening services are an effective alternative to population screening for carrier detection. Family members have a better sense and personal experience of the genetic disease in question in their family. This allows more effective genetic counseling to the couples at risk of having a child with a genetic disorder about their reproductive options. Family members at risk of being carrier for a genetic disorder can also be offered genetic counseling, based on which they choose their partners to avoid having children with genetic disorders. This approach has been applied in Pakistan for the prevention of beta-thalassemia [18]. While proposing strategies to prevent more children being born with IMD, we also acknowledge the need to address the taxes imposed on the FSMP by the Pakistan government. Pakistan is a country, where institutes like Sindh Institute of Urology and Transplant in Karachi and Shaukat Khanum Cancer Hospital in Lahore are providing free state of art medical services to patients completely supported by philanthropy. Awareness needs to be created for the IMDs among public and government to support patients and families with IMDs.

7. Conclusion

This five year report of the first Clinical Genetics Unit in Pakistan highlights the challenges in diagnosing and treating patients with IMDs in a developing country with very limited resources. Intervention strategies including tax reduction by government on FSMP and philanthropy support for the treatment of IMD patients is likely to result in better rates of continued treatment thus preventing the neurological damage sustained by these patients in the absence of treatment. Preventive strategies including prenatal genetic testing and cascade screening for at risk individuals can help in reducing the financial burden on the already stretched health care system of Pakistan.

Conflict of interest

None.

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